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(71) Applicant *(for all designated States except US)*: **THRESHOLD PHARMACEUTICALS, INC.** [US/US]; 1300 Seaport Boulevard, 5th Floor, Redwood City, California 94063 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **TIDMARSH, George** [US/US]; 45 Tintern Lane, Portola Valley, California 94028 (US). **COLOWICK, Alan** [US/US]; 1300 Seaport Boulevard, 5th Floor, Redwood City, California 94063 (US).

(74) Agents: **APPLE, Randolph, T.** et al.; Two Embarcadero Center, 8th Floor, San Francisco, California 94111-3834 (US).

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(54) Title: GLUFOSFAMIDE COMBINATION THERAPY

(57) Abstract: Glufosfamide administered alone or in combination with other chemotherapeutic agents is useful in cancer treatment.

GLUFOSFAMIDE COMBINATION THERAPY

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 60/680,451, filed 11 May 2005, the contents of which are incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present invention provides compositions and methods for treating cancer with glufosfamide in combination with anticancer agents, and generally relates to the fields of chemistry, biology, molecular biology, pharmacology, and medicine.

BACKGROUND OF THE INVENTION

[0003] Ifosfamide is a lipophilic prodrug of an alkylating agent. While ifosfamide therapies are used for treating cancer, they exhibit severe toxic side effects in patients. Ifosfamide metabolizes to chloroacetaldehyde and acrolein. In addition to hair loss and nausea/vomiting, ifosfamide metabolites chloroacetaldehyde and acrolein cause central nervous system (CNS) toxicity and bladder irritation that can lead to hemorrhagic cystitis, dysuria, and urinary frequency (see Hardman *et al.*, *Goodman & Gilman's The Pharmacological Basis of Therapeutics,* 2001, 10th Edition, McGraw-Hill, New York, 1390-6, incorporated herein by reference).

[0004] To ameliorate the bladder irritation caused by ifosfamide, mesna (mercaptoethane sulfonate sodium) is routinely administered concomitantly with ifosfamide. Mesna is an uroprotectant that specifically reduces the hemorrhagic cystitis caused by the ifosfamide metabolite acrolein. However, mesna itself can cause several side effects, including nausea, vomiting, bad taste in the mouth, diarrhea or soft stools, and headache. In addition, up to 6% of patients do not respond to mesna and still go on to develop hematuria.

[0005] Given the serious side effects caused by ifosfamide, there is a need for chemotherapy for cancer that does not involve ifosfamide. Glufosfamide, also known as α-D-glucosyl-ifosfamide mustard or glc-IPM, is a prodrug form of an alkylating agent and has been recently used in the clinic to treat cancer. See US Patent No. 6,489,302 (Wiessler *et al.*), PCT Publication No. WO 2005/07688, and PCT Application No. PCT/US2005/047314 (published as WO 2005/ _____), each incorporated herein by reference. In contrast to

ifosfamide, metabolism of glufosfamide does not release the toxic metabolite acrolein, and also produces less chloroacetaldehyde.

[0006] There remains a need for additional therapies for treatment of particular types of cancer with glufosfamide, preferably therapies that significantly improve the tumor response rate and exhibit a decrease in overall toxicity. The present invention meets such a need by providing a novel combination therapies as summarized below.

SUMMARY OF THE INVENTION

[0007] The present invention provides methods for treating cancer by administering glufosfamide alone or in combination with anticancer agents.

[0008] In one aspect the present invention provides a method for treatment of cancer comprising administering to a subject in need thereof a therapeutically effective dose of glufosfamide in combination with doxorubicin (*e.g.*, Adriamycin, Doxil and Caelyx).

[0009] In one embodiment, the invention provides a method of treating cancer comprising administering glufosfamide in combination with erlotinib (Tarceva™). In one embodiment, the invention provides a method for treating cancer, comprising administering glufosfamide, gemcitabine and erlotinib in combination to a subject in need of such treatment.

[0010] A variety of cancers can be treated by this method, for example pancreatic cancer, colorectal cancer, breast cancer, bone cancer, lung cancer, lymphoma, sarcoma, and the like.

[0011] In one aspect the present invention provides a method for treatment of doxorubicin-refractory sarcoma comprising administering to a subject in need thereof a therapeutically effective dose of glufosfamide.

[0012] As discussed above, existing combination therapies have undesirable side-effects and require coadministration of chemoprotective drugs or uroprotectants such as mesna. In contrast, metabolism of glufosfamide does not release the toxic metabolite acrolein. Thus, in one embodiment the present invention does not require coadministration of chemoprotective drugs or uroprotectants such as mesna.

BRIEF DESCRIPTION OF THE FIGURES

[0013] Figure 1 illustrates the effect of glufosfamide on the proliferation of MES-SA and MES-SA/DX5 cells.

[0014] Figure 2 illustrates the effect of Daunorubicin on the proliferation of MES-SA and MES-SA/DX5 cells.

[0015] Figure 3 illustrates the effect of Adriamycin on the proliferation of MES-SA and MES-SA/DX5 cells.

[0016] Figure 4 illustrates the results of a glufosfamide/cisplatin study in H460 lung xenograft model.

DETAILED DESCRIPTION OF THE INVENTION

[0017] The present invention arises out of the discovery that using glufosfamide alone or in combination therapies with other anti-cancer agents results in fewer side effects and eliminates the need for co-administration of additional drugs such as mesna that have their own potential side effects. Moreover, glufosfamide can be infused in patients over a shorter infusion period compared to that of ifosfamide. In some administration regimens ifosfamide is infused over a 24 hour period requiring hospitalization of patients. In one embodiment, glufosfamide is administered weekly to reduce renal toxicity.

[0018] Publications cited in this section are intended to illustrate aspects of the drug for the benefit of the practitioner; however, citation to a particular publication in this section or elsewhere in this disclosure is not intended to limit the present invention in any respect, including as to doses, combinations, and indications.

Subject

[0019] A subject is a mammal in need of treatment for cancer. Generally, the subject is a human patient. In some embodiments of the invention, the subject can be a non-human mammal such as a non-human primate, a dog, cat, rabbit, pig, etc. In some embodiments of the invention the subject can be an animal model (e.g., animals such as mice and rats used in screening, characterization and evaluation of medicaments).

Treatment

[0020] As used herein, and as well-understood in the art, "treatment" is an approach for obtaining beneficial or desired results, including clinical results. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, alleviation or amelioration of one or more symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, preventing spread of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment.

[0021] In one embodiment, the present invention provides a method for treating lymphoma wherein a therapeutically effective dose of glufosfamide is administered to a subject in need of treatment for lymphoma. In certain embodiments, the lymphoma is non-Hodgkin's lymphoma.

[0022] In one embodiment, the present invention provides a method for treating sarcoma, wherein a therapeutically effective dose of glufosfamide is administered to a subject in need of treatment for sarcoma. In certain embodiments, the sarcoma is soft tissue sarcoma. In certain embodiments, the sarcoma is non-soft tissue sarcoma. In certain embodiments, the sarcoma is chemotherapy-refractory sarcoma, such as sarcomas refractory to treatment with doxorubicin. In another embodiment the treatment is second-line treatment for sarcoma.

[0023] In one embodiment, the present invention provides a method for treating cancer comprising administering a therapeutically effective dose of glufosfamide in combination with doxorubicin. Examples of cancers that can be treated by this method include, but are not limited to, breast cancer, bone cancer, lung cancer, lymphoma, sarcoma and multiple myloma.

[0024] In one embodiment, the invention provides a method of treating cancer comprising administering to a subject in need thereof a therapeutically effective dose of glufosfamide in combination with erlotinib (e.g., Tarceva™) and optionally with another anticancer agent. In one embodiment, the invention provides a method for treating cancer, comprising administering glufosfamide, gemcitabine and erlotinib in combination to a subject in need of such treatment. A variety of cancers can be treated by this method, for example pancreatic cancer, colorectal cancer, breast cancer, lymphoma, sarcoma, lung and the like.

[0025] In one embodiment, the present invention provides a method of treatment of cancer comprising administering to a subject in need thereof a therapeutically effective dose of glufosfamide in combination with another anti-cancer agent.

[0026] Examples of anti-cancer agents include but are not limited to doxorubicin (*e.g.*, Adriamycin, Doxil and Caelyx), taxanes (*e.g.*, docetaxel and paclitaxel), imatinib mesylate (Gleevac), dacarbazine (DTIC), vincristine, topotecan, etoposide, carboplatin, rituximab, methotrexate, trastumab (Herceptin®), EGFR inhibitors (e.g., Iressa), bevacizumab, irinotecan, exatecan, pemetrexed, cisplatin, 2-deoxyglucose and rituximab.

[0027] For illustration and not limitation, description of the administration of various anticancer agents, including glufosfamide and gemcitabine for treatment of cancer is found in PCT Publication No. WO 2005/07688 and in PCT Application No. PCT/US2005/047314 (published as WO 2005 / _____), each of which is incorporated in its entirety herein.

[0028] In one embodiment, the present invention does not require coadministration of chemoprotective drugs or uroprotectants such as mesna.

Cancers

[0029] The methods of the present invention can be used for treatment of any cancer, including but not limited to breast cancer, pancreatic cancer, cancer of the colon and/or rectum, leukemia, skin cancer, bone cancer, prostate cancer, liver cancer, lung cancer, brain cancer, cancer of the larynx, gallbladder, parathyroid, thyroid, adrenal, neural tissue, head and neck, stomach, bronchi, kidneys, basal cell carcinoma, squamous cell carcinoma of both ulcerating and papillary type, metastatic skin carcinoma, osteo sarcoma, Ewing's sarcoma, veticulum cell sarcoma, rhabdomyosarcoma, Kaposi's sarcoma, osteogenic and other sarcoma, myeloma, giant cell tumor, small-cell lung tumor, gallstones, islet cell carcinoma, primary brain tumor, acute and chronic lymphocytic and granulocytic tumors, hairy-cell tumor, adenoma, hyperplasia, medullary carcinoma, pheochromocytoma, mucosal neuronms, intestinal ganglloneuromas, hyperplastic corneal nerve tumor, marfanoid habitus tumor, Wilm's tumor, seminoma, ovarian tumor, leiomyomater tumor, cervical dysplasia and in situ carcinoma, neuroblastoma, retinoblastoma, soft tissue sarcoma, malignant carcinoid, topical skin lesion, mycosis fungoide, malignant hypercalcemia, renal cell tumor, polycythermia vera, adenocarcinoma, glioblastoma multiforma, testicular, germ cell, malignant melanomas, and epidermoid carcinomas.

[0030] In one embodiment, the methods of the present invention are particularly useful for treating lymphomas, including Hodgkin's and non-Hodgkin's lymphoma.

[0031] In one embodiment, the methods of the present invention are particularly useful for treatment of sarcomas (including soft tissue sarcoma and non-soft tissue sarcoma). Methods of the present invention can be used for treatment of any sarcoma, including but not limited to, angiosarcoma, chondrosarcoma, dermatofibrosarcoma protuberens, desmoid sarcoma, Ewing's sarcoma, fibrosarcoma, gastrointestinal stromal tumor (GIST), Kaposi's sarcoma, non-uterine leiomyosarcoma, uterine leiomyosarcoma, liposarcoma, malignant fibro histiocytoma (MFH), malignant peripheral nerve sheath tumor (MPNST), osteosarcoma, osteogenic sarcoma, rhabdomyosarcoma, synovial sarcoma and veticulum cell sarcoma. In another embodiment, the present invention provides a method for treating sarcoma comprising administering glufosfamide to a subject in need of treatment of advanced and/or metastatic malignancies previously treated with chemotherapy. In certain embodiments, the

sarcoma is chemotherapy-refractory sarcoma, such as sarcomas refractory to treatment with doxorubicin.

[0032] In one embodiment, the methods of the present invention are particularly suited for treatment of pancreatic cancer, breast cancer, or colorectal cancer. Thus, in certain embodiments of the invention the subject to whom treatment is administered has colorectal cancer or metastatic colorectal cancer. In certain embodiments of the invention, the subject to whom treatment is administered has breast cancer. In certain embodiments of the invention, the subject to whom treatment is administered has pancreatic cancer. Among pancreatic cancers, chemotherapy-refractory pancreatic cancers, such as pancreatic cancers refractory to treatment with gemcitabine (see, *e.g.*, Araneo et al., 2003, *Cancer Invest.* 21:489-96; Kozuch et al., 2001, *The Oncologist* 6:488-95; Noble and Goa, 1997, *Drugs* 54: 447-72N; Stephens et al., 1998, *Oncol. Nurs. Forum* 25:87-93; Burris and Storniolo, 1997, *Eur. J. Cancer* 33: Suppl 1:S18-22; Rothenberg et al., 1996, *Ann. Oncol.* 7:347-53) can be treated using the methods disclosed herein, *e.g.*, by administration of glufosfamide in combination with erlotinib and optionally another anticancer agent. Serum carbohydrate 19-9 reportedly can be a useful marker for evaluating the response to such glufosfamide therapy in pancreatic cancer (Ziske et al., 2003, *Br. J. Cancer* 89:1413-17).

Administration Regimens

[0033] It will be appreciated that cancer treatment by chemotherapy sometimes involves multiple "rounds" or "cycles" of administration of a drug, where each cycle comprises administration of the drug one or more times according to a specified schedule (*e.g.*, daily; once per week; multiple times a week either on consecutive days or non-consecutive days; once every cycle; multiple times every cycle [for example every three weeks for three consecutive days] *etc.*, wherein each cycle ranges from 1 week up to several weeks, preferably 2, 3, 4, 5, 6, 7, or 8 weeks). For example, chemotherapeutic drugs can be administered for from 1 to 8 cycles, or for a longer period. When more than one drug (*e.g.*, two drugs) is administered to a subject, each can be administered according to its own schedule as illustrated above (*e.g.*, weekly; once every three weeks; *etc.*). It will be clear that administration of drugs, even those administered with different periodicity, can be coordinated so that both drugs are administered on the same day at least some of the time or, alternatively, so the drugs are administered on consecutive days at least some of the time.

[0034] As is understood in the art, treatment with cancer therapeutic drugs can be suspended temporarily if toxicity is observed, or for the convenience of the patient, without departing from the scope of the invention, and then resumed.

Administration in Combination

[0035] During chemotherapy treatment of cancer two, three, or four drugs can be administered to a subject "in combination" by administering them as part of the same course of therapy. A course of therapy refers to administration of combinations of drugs believed by the medical professional to work together additively, complementarily, synergistically, or otherwise to produce a more favorable outcome than that anticipated for administration of a single drug. A course of therapy can be for one or a few days, but more often extends for several weeks.

[0036] When two or more drugs are administered in combination, a variety of schedules can be used. In one case, for example and without limitation, Drug 1 is first administered prior to administration of Drug 2, and treatment with Drug 1 is continued throughout the course of administration of Drug 2; alternatively Drug 1 is administered after the initiation or completion of Drug 2 therapy; alternatively, Drug 1 is first administered contemporaneously with the initiation of the other cancer therapy. As used in this context, "contemporaneously" means the two drugs are administered the same day, or on consecutive days.

[0037] Although in principle certain drugs can be co-formulated, in general they are administered in separate compositions Similarly, although certain drugs can be administered simultaneously, more often (especially for drugs administered by infusion) drugs are co-administered, administered at different times on the same day, on consecutive days, or according to another schedule. In this context, co-administration means administration in the same course of therapy, particularly the same day.

[0038] Glufosfamide, in combination with other anti-cancer, as used in the present invention can be administered at any dose that is therapeutically effective, such as doses comparable to those routinely utilized clinically. Specific dose regimens for known and approved anti-cancer agents (e.g., the recommended effective dose) are known to physicians and are provided, for example, in the product descriptions found in the PHYSICIANS' DESK REFERENCE, 2003, 57th Ed., Medical Economics Company, Inc., Oradell, N.J; Goodman & Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS" 2001, 10th Edition, McGraw-Hill, New York; and/or are available from the Federal Drug Administration and/or are discussed in the medical literature.

[0039] In one embodiment, glufosfamide is administered for 1, 2, 3, 4, 5, 6, 7, 8, or more than 8 dosage cycles, each cycle comprises an infusion of glufosfamide in the range of:

a) about 1.0 to about 8.0 g/m^2; about 1.0 to about 6.0 g/m^2; about 1.5 to about 4.5 g/m^2; about 4.5 to about 8.0 g/m^2; about 4.5 to about 6.0 g/m^2; or about 4.5 to about 5.0 g/m^2 or over an infusion period of 1-6 hours once every three weeks;

b) about 1.0 to about 3.0 g/m^2, about 1.5 to about 3.0 g/m^2 or about 1.5 to about 2.0 g/m^2 over an infusion period of 1-6 hours for three consecutive days (days 1, 2 and 3) every three weeks;

c) about 1.0 to about 2.0 g/m^2 or about 1.5 to about 2.0 g/m^2 over an infusion period of 1-6 hours once per week; or

d) about 1.0 to about 8.0 g/m^2; about 1.0 to about 6.0 g/m^2; or about 1.5 to about 4.5 g/m^2 over an infusion period of 1-6 hours once every four weeks.

[0040] In one embodiment, glufosfamide is administered for 1, 2, 3, 4 or more than 4 dosage cycles, wherein each cycle is a seven-week cycle. In one embodiment, glufosfamide is administered for 1, 2, 3, 4, 5, 6, or more than 6 dosage cycles, wherein each cycle is a three-week cycle. In one embodiment, glufosfamide is administered for 1, 2, 3, 4, 5, 6, or more than 6 dosage cycles, wherein each cycle is a four-week cycle. In one embodiment, glufosfamide is administered weekly in the range of 1.0 to about 3.0 g/m^2, for example on Days 1 and 8 of a 21 day cycle; on Days 1, 8 and 15 of a 28 day cycle; or Days 1, 8, 15 of 21 day cycle.

[0041] As used in this context an "infusion period of 1-6 hours" includes without limitation, an infusion period of about 1, about 2, about 3, about 4, about 5 and about 6 hours.

[0042] In another embodiment, glufosfamide is administered on weeks 1, 2, 3, 5, 6 and 7 of a seven-week cycle, and the administration is for 1, 2, 3, 4, or more than 4 seven-week cycles, where each cycle comprises infusion of :

a) about 1.0 g/m^2 over a period of about 30 min;

b) about 2.2 g/m^2 over a period of about 30 min;

c) about 1.5 g/m^2 over a period of about 150 min.

[0043] In one embodiment, erlotinib is administered at about 25 mg to about 200 mg; about 100 mg to about 200 mg; about 150 mg; at least one hour after the ingestion of food. In one embodiment, erlotinib is administered two hours after ingestion of food. In one embodiment, erlotinib is administered orally.

[0044] In one embodiment, gemcitabine is administered for 1, 2, 3, 4, 5, 6, 7, 8 or more than 8 dosage cycles, and each cycle comprises an infusion of gemcitabine of:

a) about 1000 mg/m^2 over a period of about 30 min;

b) about 2200 mg/m^2 over a period of about 30 min; or

c) about 1500 mg/m^2 over a period of about 150 min.

[0045] In one embodiment, gemcitabine is administered on weeks 1, 2, 3, 5, 6 and 7 of a dosage cycle for 1, 2, 3, 4 or more than 4 dosage cycles, wherein each cycle is a seven-week cycle. In one embodiment, gemcitabine is administered on weeks 1, 2 and 3 of a dosage cycle for 1, 2, 3, 4, 5, 6, or more than 6 dosage cycles, wherein each cycle is a four-week cycle. Gemcitabine is administered one day before, one day after, or on the same day as, the administration of glufosfamide. In one embodiment, gemcitabine is administered on the same day as the administration of glufosfamide, about 30 minutes to about 4 hours after the administration of glufosfamide.

[0046] The present invention having been described in detail in the preceding sections, the following examples are provided to illustrate certain aspects of, but not to limit, the invention.

EXAMPLES

Cell Lines and Reagents

[0047] MES-SA and MES-SA/DX5 cells lines (Burkitt's lymphoma) were obtained from the American Type Culture Collection (ATCC, Rockville, MD). The cell lines were cultured in Dulbecco's modified Eagle's medium supplemented with 10% fetal calf serum, sodium pyruvate, nonessential amino acids, L-glutamine, vitamins, and antibiotics. Cells were maintained in a humidified incubator containing 5% CO_2, 21% O_2, at 37°C. All chemical reagents were purchased from Sigma Chemical Co. (St. Louis, MO) unless otherwise specified. Glufosfamide and Daunorubicin were provided directly by Threshold Pharmaceuticals, Inc. and reconstituted in PBS freshly for each study.

Example 1

Cell Proliferation Assay

[0048] To determine the effect of the combinations of the present invention on cell proliferation, the antiproliferative activity of these combinations was tested in a multi-well Alamar Blue based assay (at 3 days). Cell growth in the presence and absence of the test compound as tabulated in Table 1 was compared, as measured by a fluorescence plate reader at excitation 550 nm and emission 590 nm (see Biosource International Inc., Tech Application Notes, *Use of Alamar Blue in the measurement of Cell Viability and Toxicity*,

Determining IC_{50}). MES-SA cell line (human uterine sarcoma) (ATCC Catalog # CRL-1976), 5000 cells/well/180 μl) and its multidrug resistance variant, MES-SA/DX5 (ATCC Catalog # CRL- 1977, 5000 cells/180 μl) were seeded in a 96 well plate in RPMI medium (Invitrogen Corporation, Carlsbad, CA) and incubated overnight. After 24 hours, these plates were divided into Control group and 3 day treatment group.

[0049] A test compound (Glufosfamide, Daunorubicin, Doxorubicin) was added to each plate in the treatment groups at a concentration as tabulated in Tables 1 (in 200 μl of medium, respectively). The cells were incubated for 3 days, followed by staining with AlamarBlue. In the Control group, AlamarBlue was added to the plate at (i) day 0 and (ii) day 3 and measured to establish the control reading. In all the groups, the capacity of the cells to proliferate was measured 6 hours after addition of AlamarBlue using a fluorescence plate reader at excitation 550 nm and emission 590 nm. The results of the assay are tabulated in Tables 1 and illustrated in Figures 1-3. Dose response curves for Glufosfamide, Daunorubicin and Doxorubicin were generated, and the IC_{50} values were determined. Dose dependent percent inhibition was calculated using Graphpad Prism® (GraphPad Software, Inc.).

Table 1

Glufosfamide (μM)	Cell proliferation as % control		Daunorubicin (μM)	Cell proliferation as % control		Doxorubicin (μM)	Cell proliferation as % control	
	MES-SA	MES-SA/DX5		MES-SA	MES-SA/DX5		MES-SA	MES-SA/DX5
0 (control)	100	100	0 (Control)	100	100	0 (control)	100	100
0.8	79	84	0.00055	91	85	0.00015	78	93
2.5	77	84	0.0016	86	84	0.00045	70	94
7.4	70	75	0.0049	78	84	0.0014	70	100
22.2	64	76	0.015	68	80	0.0041	68	93
66.7	50	58	0.044	38	85	0.012	54	85
200	26	35	0.13	28	86	0.37	52	89
600	5	8	0.4	16	90	0.11	49	100
-	-	-	-	-	-	0.33	26	89
-	-	-	-	-	-	1	8	88
-	-	-	-	-	-	3	1	66

Example 2

Efficacy of Glufosfamide in the H460 lung xenograft model

H460 human lung carcinoma cells were injected subcutaneously into the flanks of female nude mice (10 mice per group). Animals were randomized to treatment groups when tumors reached approximately 100 mm^3. Control mice were treated with saline daily, IP, for

7 days. Glufosfamide was administered, IP, daily for 7 days at 50 mg/kg/day. Cisplatin (CDDP) was administered IV at 3 mg/kg once only. A final group received both Glufosfamide and CDDP. As illustrated in Figure 4, CDDP alone resulted in a 43% reduction in tumor growth at study termination compared to control ($P < 0.05$). Glufosfamide alone reduced tumor growth by 55% ($P < 0.05$). The combination of Glufosfamide and CDDP resulted in a 66% reduction in tumor growth ($P < 0.01$ vs vehicle). These results indicate that Glufosfamide alone is effective in reducing tumor growth and that combining Glufosfamide with CDDP is more effective than either treatment alone.

Equivalents and Incorporation by Reference

[0050] While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes can be made and equivalents can be substituted without departing from the scope of the invention. In addition, many modifications can be made to adapt a particular situation, material, composition of matter, process, process step or steps, to achieve the benefits provided by the present invention without departing from the scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto.

[0051] All publications and patent documents cited herein are incorporated herein by reference as if each such publication or document was specifically and individually indicated to be incorporated herein by reference. Citation of publications and patent documents is not intended as an indication that any such document is pertinent prior art, nor does it constitute any admission as to the contents or date of the same.

Claims:

1. A method of treating sarcoma comprising administering to a subject in need thereof a therapeutically effective dose of glufosfamide.

2. The method of claim 1 wherein the sarcoma is a soft tissue sarcoma.

3. The method of claim 1 wherein the sarcoma is a non-soft issue sarcoma.

4. The method of claim 1 wherein the sarcoma is doxorubicin-refractory sarcoma.

5. A method of treating cancer comprising administering to a subject in need thereof a therapeutically effective dose of glufosfamide in combination with doxorubicin.

6. The method of claim 5 wherein the cancer is sarcoma.

7. A method of treating cancer comprising administering glufosfamide and erlotinib in combination to a subject in need of treatment for cancer.

8. The method of claim 7 further comprising administering a therapeutically effective dose of gemcitabine.

9. The method of claim 7 or claim 8 wherein the cancer is locally advanced and/or advanced metastatic advanced solid tumor.

10. The method of claim 7 wherein the cancer is pancreatic cancer.

11. The method of claim 10 wherein the cancer is a gemcitabine-refractory pancreatic cancer.

12. The method of any one claims 1-11 wherein glufosfamide is administered for one or more dosage cycles, each cycle comprising infusion in the range of:

a) about 1.5 to about 8.0 g/m^2; about 1.5 to about 6.0 g/m^2; about 1.5 to about 4.5 g/m^2; about 4.5 to about 8.0 g/m^2; about 4.5 to about 6.0 g/m^2; or about 4.5 to about 5.0 g/m^2 or over an infusion period of 1-6 hours once every three weeks;

b) about 1.5 to about 3.0 g/m^2 or about 1.5 to about 2.0 g/m^2 over an infusion period of 1-6 hours for three consecutive days (days 1, 2 and 3) every three weeks;

c) about 1.5 to about 2.0 g/m^2 over an infusion period of 1-6 hours once per week; or

d) about 1.5 to about 8.0 g/m^2; about 1.5 to about 6.0 g/m^2; or about 1.5 to about 4.5 g/m^2 over an infusion period of 1-6 hours once every four weeks.

FIGURE 1

Effect of Glufosfamide on proliferation of MES-SA and MES-SA/DX5 cells

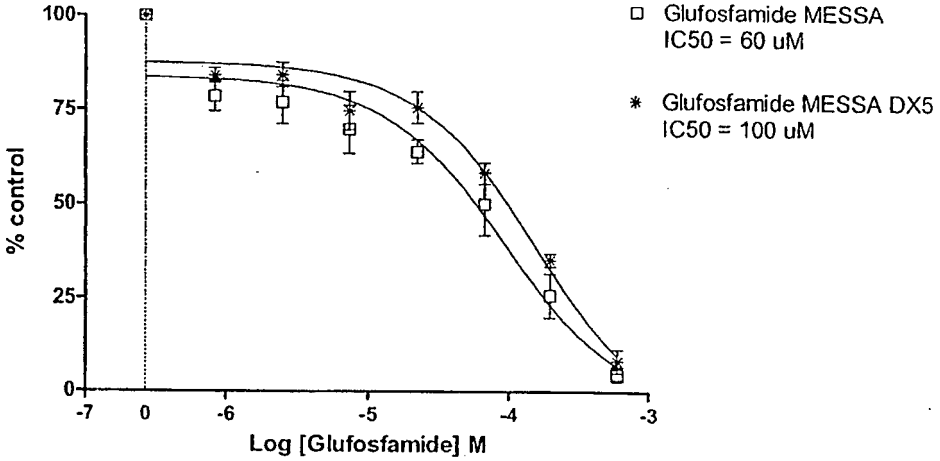


FIGURE 2

Effect of Daunorubicin on proliferation of MESSA and MESSA/DX5 cells

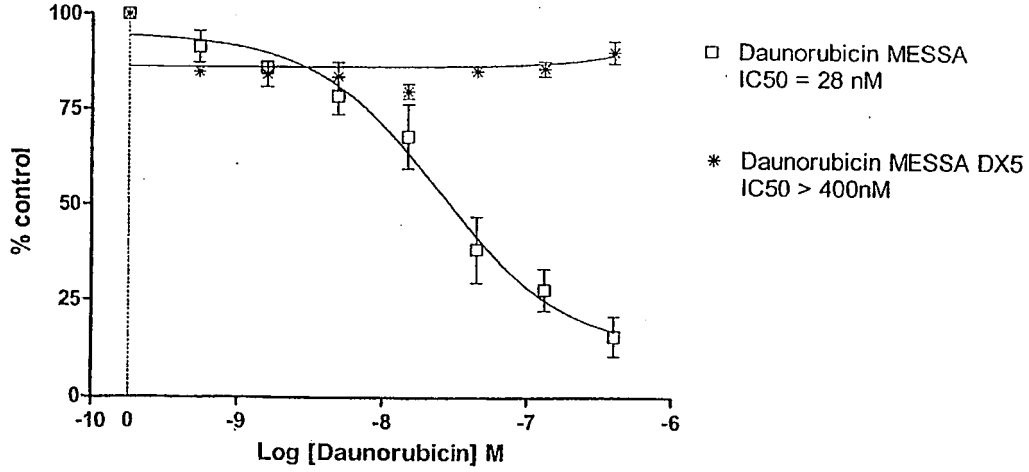


FIGURE 3

Effect of Adriamycin on proliferation of MES-SA and MES-SA/DX5 cells

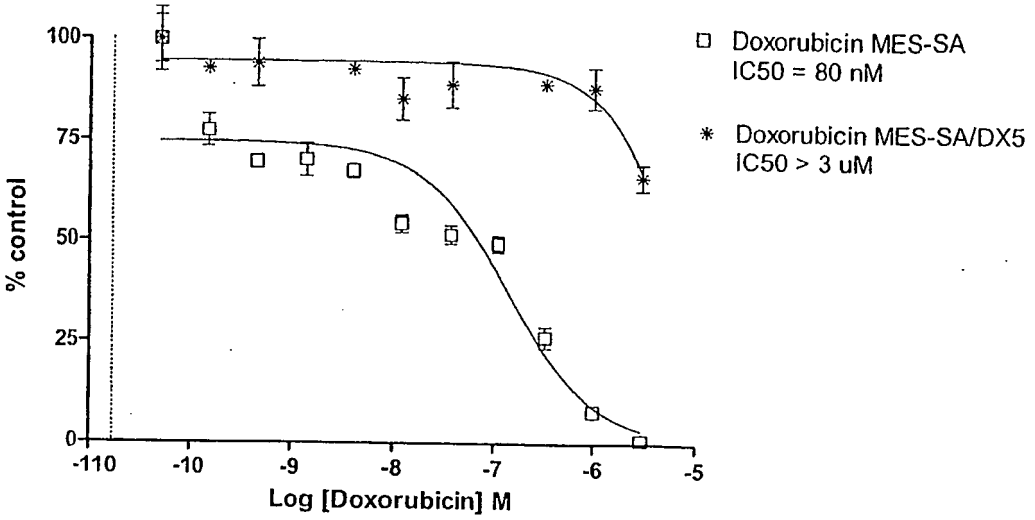
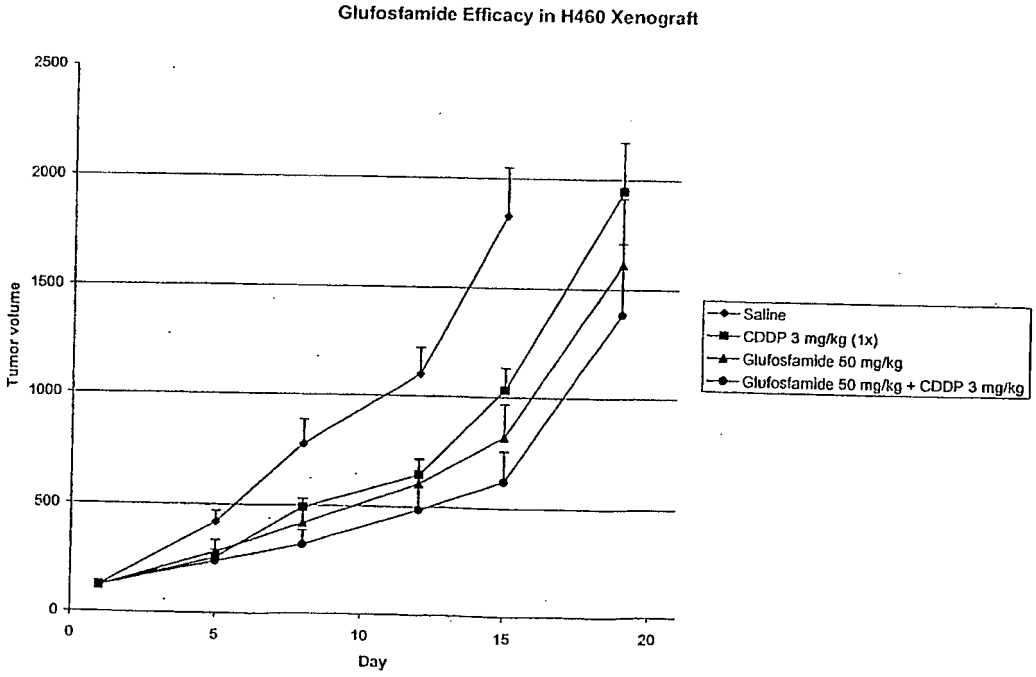


FIGURE 4

Results of a glufosfamide/cisplatin study in H460 lung xenograft model.



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US06/18191

A. CLASSIFICATION OF SUBJECT MATTER
IPC: A01N 43/04(2006.01);A61K 31/70(2006.01)

USPC: 514/23,25
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/23, 25

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN - registry, caplus; EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,622,936 (WIESSLER et al.) 22 April 1997 (22.04.1997), whole document, especially compound 28 in figure 2.	1 --- 2-4

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (571) 273-3201

Authorized officer
Traviss C. McIntosh
Telephone No. 571-272-0700

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